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FILING DATE: *March 26, 2004*
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Certified by

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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☑ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

CLORETAZINE POTENTIATION OF ANTI-TUMOR NUCLEOSIDES EFFECT

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS ***(check all that apply)***

☑ Specification *Number of Pages* 8
☐ Drawing(s) *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify) Express Mail Certificate of Mailing bearing Label EV 333072516 US, claims (1 page)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: ______

Respectfully submitted,

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number	891-PRO

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Number 2 of 2

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Dkt. #891-PRO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	KING, et al.
U.S. Serial No.:		Not Yet Known
Filed	:	Herewith
For	:	CLORETAZINE POTENTIATION OF ANTI-TUMOR NUCLEOSIDES EFFECT

Law Offices of Albert Wai-Kit Chan, LLC
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March 26, 2004

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Dkt. #891-PRO

Application
for
United States Letters Patent

To all whom it may concern:

Be it known that **Ivan KING, Mario SZNOL, Michael F. BELCOURT, and Li-mou ZHENG**

have invented certain new and useful improvements in

CLORETAZINE POTENTIATION OF ANTI-TUMOR NUCLEOSIDES EFFECT

of which the following is a full, clear and exact description.

BACKGROUND

Deoxyribonucleic acid (DNA) alkylating agents are a component of many standard treatment regimens for hematologic malignancies. Although grouped together as a class of agents, individual alkylating agents may be distinguished by the type of DNA damage, the specificity for attacking DNA versus other cellular components, the mechanisms by which the cell repairs the particular type of DNA damage, and entry into and disposition of the drug within the tumor and normal cells. Continued preclinical efforts to understand mechanisms of action has led to synthesis of novel compounds with the potential for improved anti-tumor activity and a superior safety profile compared to currently available agents.

CLORETAZINE™ {VNP40101M, 101M, 1,2-bis(methylsulfonyl)-1-(2-chloroethyl)-2-(methylamino)carbonylhydrazine} was selected as the lead clinical development candidate from a group of sulfonylhydrazine prodrugs that are potent alkylating agents and have broad anti-tumor activity in animal models (1-5). The specific properties that led to testing of this compound are as follows:

1. Metabolism leads to a high yield of hard chloroethylating species (6).
2. VNP40101M is a relatively specific O^6 guanine chloroethylator, producing minimal or no alkylation of the N^7 position of guanine, and minimally inducing single strand DNA breaks, thus maximizing DNA damage associated with anti-tumor activity and minimizing damage associated with toxicity (6).
3. VNP40101M metabolism yields a methyl-isocyanate that inhibits the cellular enzyme O^6 alkylguanine DNA alkyltransferase (AGT), which removes the initial mono-adducts in DNA and prevents cross-linking. VNP40101M was shown to be active against a mer+ (AGT-expressing) cell line (7).
4. VNP40101M demonstrated activity *in vitro* against cell lines with high glutathione and glutathione transferase activity, which are known mechanisms of resistance to alkylating agents (8).
5. Although its solubility is modest, VNP40101M has increased solubility compared to other agents in this class (9).

Activity in Murine Tumor Models

VNP40101M has shown broad anti-tumor activity against leukemia and solid syngeneic and human xenograft tumors in murine models (1-5). The data is summarized briefly below:

1. Against intraperitoneal (IP) implanted L1210 leukemia (10^6 tumor cells) that is resistant to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), cyclophosphamide, or melphalan, a single dose of VNP40101M administered IP 24 hours after tumor inoculation (20-60 mg/kg, or 60-180 mg/m^2) was curative in 100% of mice (survival ≥ 60 days). The VNP40101M doses required to produce long-term survival in sensitive and resistant L1210-bearing mice were only modestly myelosuppressive when administered to non-tumor-bearing mice. Higher single doses (80-100 mg/kg) produced signs of a wasting condition and death in some animals, which occurred > 50 days after treatment. When administered IP daily for 6 days, VNP40101M at a dose of 6 mg/kg/d (total dose 36 mg/kg) increased life span of treated mice by 333% compared to control mice, and at doses of 12-18 mg/kg/d (total doses of 72- 108 mg/kg) was curative in 100% of animals. Delayed toxic deaths were not observed with the d x 6 schedule, however, total doses higher than 108 mg/kg were not tested.
2. Against subcutaneous tumors of the human U251 glioma staged to ~300 mg in nude mice, VNP40101M administered as 10 mg/kg q2d x 11 or 20 mg/kg q4d x 6 IP caused complete regressions.
3. Against the murine M109 lung carcinoma implanted subcutaneously and staged to ~150 mg, VNP40101M administered as 10 mg/kg q2d x 10 or 20 mg/kg q4d x 5 IP delayed tumor growth, with the latter schedule delaying time to reach 1 gram by 14 days.
4. Administration of VNP40101M weekly by the IP route produced significant delays in tumor growth against the syngeneic B16F10 melanoma and against the human HTB177 lung and WiDr colon carcinoma cell lines. Doses from 10–60 mg/kg were active, but higher doses produced greater growth inhibition.
5. Substantial anti-tumor activity was observed by IP administration of VNP40101M against intra-cranially implanted L1210 leukemia, demonstrating good penetration through the blood-brain barrier.

Toxicology Studies

The relationship between VNP40101M dose and white blood cell count (WBC) was examined in normal CD_2F_1 mice. Modest leukopenia (50% of baseline) was observed with a single IP dose of 40 mg/kg (120 mg/m^2). VNP40101M doses of 60-80 mg/kg reduced WBC counts to approximately 25 and 15% of baseline, respectively, by day 4 with full recovery by day 21. As noted in section 1.2.A, high single doses of 80-100 mg/kg administered IP to tumor-bearing mice produced signs of a wasting condition and deaths occurring > 50 days after treatment.

Toxicology studies were performed in rats. A dose of 3 mg/kg (18 mg/m^2), when given intravenously (IV) on a d x 5 dosing schedule, produced no clinical signs or symptoms on day 15, but 2/10 rats had lung findings on day 29, including a small amount of thoracic cavity fluid and failure of the lung to collapse. Microscopic findings at the 3 mg/kg (d x 5) dose level were primarily limited to the lung and included alveolar edema, congestion, alveolar histiocytosis, and vascular thrombi. The higher dose of 10 mg/kg (60 mg/m^2) d x 5 produced few significant gross necropsy findings on day 15, but thoracic cavity fluid was found in approximately 50% of animals sacrificed on day 29 and 6/6 animals sacrificed on days 30/31. Histopathologic findings in the lung were similar to those observed at the 3 mg/kg dose level. For doses as high as 10 mg/kg d x 5, myelosuppression was not observed. Effects on serum chemistries were limited to decreases in total protein and albumin, which were observed on day 29 in the 10 mg/kg dose group.

In toxicology studies performed in dogs, single doses of 1, 3, 10, and 30 mg/kg were administered intravenously. The 1 and 3 mg/kg doses were well-tolerated and produced minimal clinical signs through at least 21 days of observation. The higher doses of 10 and 30 mg/kg (200 and 600 mg/m^2, respectively) produced marked clinical signs, as well as laboratory abnormalities including increased alkaline phosphatase, decreased albumin, increased bilirubin, increased creatine phosphokinase, and decreased white and red blood cell counts. Toxicity was also assessed for 0.3, 1 and 3 mg/kg doses administered intravenously daily x 5. The 3 mg/kg d x 5 dose produced marked clinical signs including reduced activity, loose stool, anorexia and slight dehydration, requiring sacrifice of the animals on day 8. There was also marked leukopenia by day 8, and slight elevation of the alkaline phosphatase. A dose of 1 mg/kg (20 mg/m^2) d x 5 produced minimal clinical signs and symptoms, and only a mild leukopenia on day 8 that recovered to baseline by day 15.

Phase I Studies of VNP40101M

VNP40101M has been studied in two phase I trials conducted in patients with advanced solid tumors or hematologic malignancies. In the first phase I trial, 26 patients with solid tumors were treated by IV infusion over 15-30 minutes at dose levels ranging from 3-305 mg/m^2 every 4-6 weeks. The maximum tolerated dose (MTD) was 305 mg/m^2. Among the seven patients treated at the MTD, six developed grade 3 thrombocytopenia. The platelet nadir occurred between days 25-33. Five of the patients treated at the MTD developed ≥ grade 2 granulocytopenia, but only one patient had a grade 3 event. Hematologic toxicities recovered to ≤ grade 1 between days 32-45. No dose-limiting non-hematologic toxicities were observed.

A second phase I trial is being conducted at the MD Anderson Cancer Center in patients with advanced hematologic malignancies. Twenty-eight patients with relapsed or refractory leukemia (20 acute myeloid leukemia [AML], 3

myelodysplasia, 1 chronic myeloid leukemia in blast crisis, 3 acute lymphocytic leukemia, 1 chronic lymphocytic leukemia) have been accrued to the study at doses ranging from 220-708 mg/m^2. Through the dose of 708 mg/m^2, no dose-limiting non-hematologic toxicities were observed. At doses ≥ 400 mg/m^2, patients developed a transient infusion-related syndrome consisting of headache, nausea, vomiting, myalgias/cramps, facial flushing, dizziness, tachycardia, and hypotension. The infusion-related reaction was self-limited and resolved within several hours after completing treatment in all patients. Among the seven patients treated at 708 mg/m^2, one patient developed prolonged marrow aplasia (> 80 days) without evidence of leukemia. Thus, myelosuppression may be a dose-limiting toxicity (DLT) at 708 mg/m^2. An additional cohort of patients is currently being evaluated at an interim dose of 600 mg/m^2.

Evidence of anti-tumor activity was observed in patients with advanced hematologic malignancies. One previously untreated patient with high-risk myelodysplasia developed a complete response by day 28 after a single course of VNP40101M administered at 300 mg/m^2. Although no other patient achieved complete remission, VNP40101M reduced peripheral blood blasts at least transiently in most patients at all dose levels. In addition, a heavily pre-treated patient with AML had substantial clearing of marrow blasts and resolution of gingival leukemic infiltration at a dose of 220 mg/m^2, and a patient with AML treated at 532 mg/m^2 had reduction in marrow blasts and improvement of neutrophil counts by day 28. The level of activity warrants further exploration of VNP40101M alone and in combination in patients with AML.

Rationale for the Current Combination of VNP40101M with nucleoside analogs such as Cytarabine (cytosine arabinoside, AraC) in Hematologic Malignancies

1. An agent with intense myelosuppressive properties associated with minimal extramedullary toxicities is of major interest in patients with leukemia. Cytarabine, a cell-cycle specific antimetabolite, is the most effective drug in the treatment of AML. Cytarabine is phosphorylated intracellularly and incorporated into DNA. By inhibiting DNA polymerases and DNA synthesis, cytarabine is predicted to inhibit DNA repair and enhance the cytotoxicity of VNP40101M.

2. Other nucleoside analogs that are capable of inhibiting DNA synthesis or incorporating into DNA such as azacitidine, cladribine, decitabine. gemcitabine, mercaptopurine, thioguanine, fludarabine, clofarabine, troxacitabine, and pentostatin are useful to combine with VNP40101M to treatment hematologic malignancies.

3. Hematologic malignancies include acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphoblastic leukemia, chronic myelogenous

leukemia, myelodysplasia, hairy cell leukemia, Hodgkin's disease and non-Hodgkin's disease.

Example 1
In vitro cytotoxicity of CLORETAZINE and AraC on tumor cell lines

The cytotoxicity of the combination of CLORETAZINE and nucleoside analogs on tumor cell lines is examined using a cell viability assay. Several leukemia cell lines (L1210 and HL-60) and lymphoma cell lines (Raji and Namalwa) are exposed to CLORETAZINE, alone or in combination with various concentrations of ara-C. After 72 hours, the remaining viable cells were quantified by measuring mitochondrial oxidoreductase activity. Concentrations of AraC used are between 0.1 to 100 uM; concentrations of CLORETAZINE used are between 20 to 500 uM. Dose-effect analyses (combination index) showing combination effects of CLORETAZINE and AraC are analyzed. Combination indices of 0.75 – 0.8 and 0.1 – 0.3 indicate moderate synergism and strong synergism, respectively. Based on the in vivo activity, synergistic effects are expected for CLORETAZINE and AraC on killing tumor cells.

Example 2
In vitro cytotoxicity of CLORETAZINE and Fludarabine on tumor cell lines

The cytotoxicity of the combination of CLORETAZINE and nucleoside analogs on tumor cell lines is examined using a cell viability assay. Several leukemia cell lines (L1210 and HL-60) and lymphoma cell lines (Raji and Namalwa) are exposed to CLORETAZINE, alone or in combination with various concentrations of Fludarabine. After 72 hours, the remaining viable cells were quantified by measuring mitochondrial oxidoreductase activity. Concentrations of Fludarabine used are between 0.1 to 100 uM; concentrations of CLORETAZINE used are between 20 to 500 uM. Dose-effect analyses (combination index) showing combination effects of CLORETAZINE and Fludarabine are analyzed. Combination indices of 0.75 – 0.8 and 0.1 – 0.3 indicate moderate synergism and strong synergism, respectively.

Example 3
In vivo antitumor activity of CLORETAZINE and AraC on leukemia

Eighty Female Balb/c x DBA/2 (CD_2F1) mice were inoculated intraperitoneally (ip) on day 0 with $1x10^6$ L1210 cells in 0.2mL phosphate-buffered-saline (PBS). The mice were randomly divided into 8 groups; each group consisted of 10 mice. The animals were untreated or treated with a single bolus dose of Cloretazine at 5, or 10mg/kg, ip, on day 1 with or without AraC (50mg/kg, ip) on days 1, 3, 5, 7, and 9. During the experiments, mice were observed daily for survival. It was determined that mice that survive for more than 60 days after inoculation of L1210 cells might be regarded as long-term survivors. Kaplan-Meier plots were generated, and survival time of animals was analyzed using student T-test. Significance was defined as $P < 0.05$.

The results presented in Table 1 showed that intraperitoneal inoculation of mice with $1x10^6$ L1210 leukemia cells resulted in a rapid development of ascites followed by death of all animals in untreated control within 18 days and in AraC treatment control within 30 day. CLORETAZINE treatment at single doses of 5 and 10mg/kg increased long-term survivors to 50% and 90%, respectively. Therapeutic efficacies of combinational treatments were superior to single agents. CLORETAZINE, at 5 and 10mg/kg, plus AraC treatments increased long-term survivors to 80% and 100%, respectively.

Table 1 Therapeutic efficacy of single agents vs. combinations

Group	Long-term Survivors (%)	P value*
1. Untreated Control	0	
2. AraC 50mpk	0	
4. 101M 5mpk	50	
5. 101M 10mpk	90	
7. AraC 50mpk+101M 5mpk	80	0.0024
8. AraC 50mpk+101M 10 mpk	100	0.0022

*Combinational therapy against 101M at corresponding doses

Example 4
In vivo antitumor activity of CLORETAZINE and fludarabine on leukemia

Eighty Female Balb/c x DBA/2 (CD_2F1) mice are inoculated intraperitoneally (ip) on day 0 with 1 $x10^6$ L1210 cells in 0.2mL phosphate-buffered-saline (PBS). The mice are randomly divided into 8 groups; each group consists of 10 mice. The animals are untreated or treated with a single bolus dose of CLORETAZINE at 5, or 10mg/kg, ip, on day 1 with or without fludarabine (1- 20 mg/kg, ip) on multiple days between days 1 to 9. During the experiments, mice are observed daily for survival. It is determined that mice that survive for more than 60 days after inoculation of L1210 cells might be regarded as long-term survivors. Kaplan-Meier plots are generated, and survival time of animals is analyzed using student T-test. Significance is defined as $P < 0.05$.

Example 5
Use of CLORETAZINE and cytarabine in patients with AML

Cytarabine is administered by IV continuous infusion at a dose of 0.5 to 3.0 $gm/m^2/day$ for one to six days. Preferably, Cytarabine is administered at a dose of 1.0 to 2.0 $gm/m^2/day$ for three to four days. CLORETAZINE is administered over 15-30 minutes on day 1 to day 3 prior to the cytarabine infusion. The dose of CLORETAZINE is between 200 to 700 mg/m^2. Preferably, CLORETAZINE is

administered on day 1 prior to the cytarabine infusion and the dose is between 450 to 650 mg/m^2. Multiple cycles of treatment can be repeated.

Example 6
Use of CLORETAZINE and fludarabine in patients with lymphoma

Fludarabine is administered by IV continuous infusion at a dose of 5 to 40 mg/m^2/day for one to six days. Preferably, fludarabine is administered at a dose of 15 to 25 mg/m^2/day for five consecutive days. CLORETAZINE is administered over 15-30 minutes on day 1 to day 3 prior to the fludarabine infusion. The dose of CLORETAZINE is between 200 to 700 mg/m^2. Preferably, CLORETAZINE is administered on day 1 prior to the fludarabine infusion and the dose is between 450 to 650 mg/m^2. Multiple cycles of treatment can be repeated.

10. REFERENCES

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What is claimed is:

1. A method for treating or preventing tumor in a subject comprising administering to the subject an effective amounts of:
   (1) cloretazine, or its functional equivalent; and
   (2) a nucleoside, a nucleoside analog or its functional equivalent.

2. A method for inhibiting tumor cell growth comprising contacting the tumor cell with effective amounts of:
   (1) cloretazine, or its functional equivalent; and
   (2) a nucleoside, a nucleoside analog or its functional equivalent.